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Resveratrol ameliorates depressive-like behavior in repeated corticosterone-induced depression in mice

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ABSTRACT

A mouse model of depression has been recently developed by exogenous corticosterone (CORT) administration, which has shown to mimic HPA-axis induced depression-like state in animals. The present study aimed to examine the antidepressant-like effect and the possible mechanisms of resveratrol, a naturally occurring polyphenol of phytoalexin family, on depressive-like behavior induced by repeated corticosterone injections in mice. Mice were injected subcutaneously (s.c.) with 40 mg/kg corticosterone (CORT) chronically for 21 days. Resveratrol and fluoxetine were administered 30 min prior to the CORT injection. After 21-days treatment with respective drugs, behavioral and biochemical parameters were estimated. Since brain derived neurotrophic factor (BDNF) has been implicated in antidepressant activity of many drugs, we also evaluated the effect of resveratrol on BDNF in the hippocampus. Three weeks of CORT injections in mice resulted in depressive-like behavior, as indicated by the significant decrease in sucrose consumption and increase in immobility time in the forced swim test and tail suspension test. Further, there was a significant increase in serum corticosterone level and a significant decrease in hippocampus BDNF level in CORT-treated mice. Treatment of mice with resveratrol significantly ameliorated all the behavioral and biochemical changes induced by corticosterone. These results suggest that resveratrol produces an antidepressant-like effect in CORT-induced depression in mice, which is possibly mediated by rectifying the stress-based hypothalamic–pituitary–adrenal (HPA) axis dysfunction paradigm and upregulation of hippocampal BDNF levels.

1. Introduction

Depression is a chronic, multi-factorial psychiatric disorder which can be debilitating and even life threatening [1,2]. With a lifetime prevalence in the range of 1.5–19.0% and a median estimate of 9.4% [3], it is projected to become the second leading cause of disability worldwide by 2030 [4]. Depression emerges as a serious health concern when there are enduring episodes of low mood, anhedonia, altered pattern of sleep and appetite, retardation or psychomotor agitation, and at its worst, suicidal tendency [5].

Stressful life events have demonstrated a substantial causal association with depression and stress paradigms have long been used to model the disease [6–8]. Several findings have shown hypothalamic–pituitary–adrenal (HPA) axis dysfunction in stress-related illnesses, including depression [9,10]. The HPA axis is activated in response to stress, which results in increased concentration of glucocorticoids in the circulating blood [11,12]. Under normal condition, blood glucocorticoid level is tightly regulated by a negative feedback mechanism. However, high concentration of blood glucocorticoids is reportedly maintained in patients with depression as compared to healthy controls due to a dysfunction in the feedback mechanism [13,14]. In this context, patients with Cushing's disease or those undergoing long-term pharmacotherapy with glucocorticoids exhibit an extremely high rate of depression [15]. On the other hand, a lowered expression of brain derived neurotrophic factor (BDNF), a critical regulator of synaptic plasticity was reported in mental disorders through its interaction with the glucocorticoid system [16].

A stress-based animal model by repeated corticosterone (CORT) treatment has been performed widely in adult rodents, which resulted in depressive-like behavior marked by significant changes in behavioral traits, neurochemistry and brain [11,17,18]. These findings suggest that a chronic corticosterone treated rodent model is suitable for evaluating the efficacy of potential antidepressant candidates and to explore the mechanism of action of antidepressants.

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The existing armamentarium of clinical antidepressants includes tricyclic antidepressants, monoamine oxidase inhibitors, and noradrenaline and serotonin reuptake inhibitors. However, these drugs fail to deal with the multiple pathogenic factors involved in depression, with many showing truncated response rates and often causing undesirable side effects such as cardiotoxicity, hypertensive crisis, sexual dysfunction and sleep disorder [19]. This necessitates the development of safe, better tolerated and effective pharmacotherapeutics, and one such promising class of drugs is plant based natural products.

Resveratrol (3,5,4′-trihydroxystilbene) (Fig. 1) is a naturally occurring polyphenol of phytoalexin family; found in grapevines, pines, legumes as well as in the roots of Japanese knotweed/Itadori plant (*Polygonum cuspidatum*); and produced in response to injury or when the plant is under attack by pathogens such as bacteria or fungi [20,21]. Pharmacological studies have demonstrated antioxidant [22], anti-inflammatory [23], anti-diabetic [24], cancer chemopreventive [25], cardio-protective [21] and neuroprotective [26] properties as well as the capacity to inhibit the development of osteoporosis [27] and menopausal symptoms [28]. Moreover, it is reported to influence the metabolism of monoamines, particularly 5-HT and noradrenaline, to restore normal monoaminergic function and produce antidepressant-like activity in a mouse model of behavioral despair [29]. Therefore, in this study, the antidepressant-like effect of resveratrol treatment was further evaluated in a mice model of depression induced by repeated injections of corticosterone (CORT), the rodent homologue of cortisol, the principal human glucocorticoid. Given that BDNF is involved in the molecular pathophysiology of depression, we also investigated whether the antidepressant-like effect of resveratrol was related to the modulation of BDNF expression in brain.

2. Materials and methods

2.1. Animals

All the animal experiment protocols were approved by the Institutional Animal Ethics Committee, Gauhati Medical College & Hospital (CPCSEA Registration No. 351; 3/1/2001). Experiments were performed on male Swiss albino mice aged 4–6 weeks, weighing 25–30 g, procured from Pasteur Institute, Shillong, India. Animals housed in polypropylene cage containing sterile paddy husk as bedding were maintained at 22 ± 2 °C and a 50–60% relative humidity, under a 12:12 h light/dark cycle throughout the experiment. Standard laboratory animal feed and water were provided *ad libitum*. Before experiment, animals were subjected to an acclimatization period of one week and then randomly subjected to the experiment.

2.2. Chemicals

Corticosterone, Resveratrol and Fluoxetine were purchased from Sigma–Aldrich, St. Louis, MO, USA. Corticosterone ELISA kit was purchased from Abnova Corporation, Walnut, CA, USA and hippocampal BDNF ELISA kit was purchased from Promega Corporation, Madison, WI, USA. All other chemicals and reagents were of analytical grade.

2.3. Experimental design

Animals were divided into four groups of eight animals each. The detailed experimental design is depicted in Fig. 2. Resveratrol and fluoxetine were administered 30 min prior to the CORT injection for 21 days. The doses and time of administration

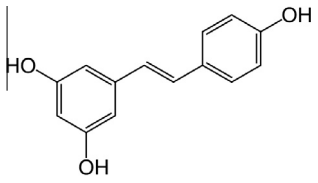

Fig. 1. Structure of resveratrol.

were selected based on literature data and dose–response pilot studies [30]. All behavioral tests were conducted between 9.00 a.m. and 04.00 p.m. in a noise-free, illumination controlled room and the readings were recorded by an observer blind to the treatments administered.

2.4. Sucrose preference test

The sucrose preference test (SPT) was carried out 24 h after the last drug treatment. The test was performed as described previously [31]. The mice were trained to adapt to sucrose solution (1%, w/v) 72 h before the test. Briefly, two bottles of 1% sucrose solution were placed in each cage for 24 h, then later one of the bottles was replaced with water for 24 h. To avoid possible effects of side preference in drinking behavior, the location of the bottles was switched after 12 h. After the adaptation, mice were deprived of water and food for 24 h. Sucrose preference test was conducted at 9:00 a.m. in which the mice were housed in individual cages and given free access to the two bottles containing 100 ml of sucrose solution (1%, w/v) and 100 ml of water, respectively. After 24 h, the volume (ml) of both the consumed sucrose solution and water were recorded and the sucrose preference was calculated by the following formula:

$$\text{Sucrose preference} = \text{sucrose consumption (ml)}/(\text{water consumption (ml)} + \text{sucrose consumption (ml)}) \times 100$$

2.5. Forced swim test

The forced swim test (FST) was carried out 48 h after the sucrose preference test and the method employed was similar to that described previously [32]. Briefly, individual mouse were subjected to swimming stress session for 15 min (pre-test), in a vertical plastic cylinder (25 cm high, 14 cm in diameter) containing 10 cm of water, maintained at 25 ± 2 °C. After 24 h, FST was carried out and the total duration of immobility (seconds) was recorded during the last 4 min of a single 6-min test session. A mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only small movements necessary to keep its head above water. The water in the container was changed after each trial.

2.6. Tail suspension test

The tail suspension test (TST) based on the method described previously [33], was carried out 24 h after the FST. Mice both acoustically and visually isolated were suspended 50 cm above the floor by means of an adhesive tape, placed approximately 1 cm from the tip of the tail. The total duration of immobility (seconds) was quantified during a test period of 6 min. Mice were considered immobile only when they hung passively and completely motionless.

2.7. Sample collection for biochemical parameters

Twenty-four hours after completion of TST, the mice were sacrificed by cervical dislocation. Whole blood was collected and